

Disposition of high-dose busulfan in pediatric patients undergoing bone marrow transplantation

We studied the pharmacokinetics of busulfan (16 mg/kg) in 16 pediatric patients affected by malignant and nonmalignant disorders between 6 months and 19 years of age (mean \pm SD, 5.7 ± 6.5 years) who were undergoing allogeneic (15 patients) and autologous (one patient) bone marrow transplantation. In all children, the conditioning regimen consisted of busulfan given orally at a dose of 1 mg/kg every 6 hours for 16 doses (total dose, 16 mg/kg), associated with other drugs. The pharmacokinetics of busulfan was studied during the 6-hour dosing interval on the third day of therapy by use of a high-performance liquid chromatographic assay. The value for the time to reach maximum concentration, expressed as mean \pm SD, was 1.1 ± 0.5 hour; maximum concentration was 609.6 ± 225.3 ng/ml; steady-state concentration was 358.9 ± 135.5 ng/ml; area under the plasma concentration-time curve was 2153.6 ± 813.1 ng \cdot hr/ml; oral clearance was 0.535 ± 0.226 L/hr/kg; and half-life was 2.4 ± 0.8 hours. Age-related differences in busulfan disposition were observed. The mean busulfan oral clearance in a group of 10 patients with an age range from 6 months to 3 years was 0.619 L/hr/kg, whereas six patients whose ages ranged from 7 to 19 years had a oral clearance of 0.396 L/hr/kg. The half-lives for busulfan during infancy decrease continuously until early childhood but were prolonged in older children. No significant relationship between systemic exposure to busulfan and drug effect was observed. (CLIN PHARMACOL THER 1993;53:45-52.)

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Bone marrow transplantation represents a curative treatment for children affected by inborn errors of the immune system, such as Fanconi's anemia or hemoglobinopathies, and for patients with acquired diseases, such as severe aplastic anemia and acute or chronic leukemias.¹⁻⁴ Drugs used in conditioning regimens to prepare patients before bone marrow transplantation are essential in determining the outcome. In allogeneic bone marrow transplantation, myeloablative therapy has three goals: (1) to create space for the donor marrow (displacement effect), (2) to determine

sufficient suppression of the recipient immune system to avoid rejection of the infused hemopoietic stem cells, and (3) in the case of leukemia, to eradicate the clonal neoplastic population. Meanwhile, the only goal of autologous bone marrow transplantation is to destroy the clonogenic malignant cells of the patient.⁵

Most conditioning regimens are still combined modalities of chemotherapy plus radiotherapy derived from the original Seattle regimen,⁶ consisting of total body irradiation and cyclophosphamide, which is considered to be the standard term of comparison.

However, given the untoward side effects and the still significant incidence of relapse for conditioning regimens of total body irradiation, alternative myeloablative therapies, consisting of chemotherapy alone, have been explored.

Busulfan, a highly myelotoxic agent, has been widely used in conditioning regimens of patients affected by malignant and nonmalignant conditions.⁷⁻¹⁰ In children, when compared with radiotherapy, conditioning regimens based on the use of busulfan seem

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to be associated with an equivalent antileukemic effect, a slight decrease in full donor marrow chimerism and with lower early and late toxicity.¹⁰⁻¹² Several authors have suggested that toxicity or engraftment failure may be attributable to interindividual variability in drug disposition¹³ or busulfan underdosing in children when the classic busulfan regimens used in adults are adopted. A crucial issue in children is represented by long-term side effects of busulfan. Endocrinologic problems are of particular importance and the object of both retrospective and perspective recently published studies.¹⁴⁻¹⁵

Therefore there is currently considerable interest in measurement and interpretation of busulfan concentration in plasma. Much of this interest derives from the hope that such measurements will provide a means of controlling drug therapy to achieve a better antileukemic effect, to enhance the likelihood of donor engraftment, and to decrease toxicity. The aim of this study was to evaluate the pharmacokinetic parameters of busulfan in pediatric patients affected by different malignant and nonmalignant disorders.

PATIENTS AND METHODS

Patients. Between March 1989 and December 1991, 16 patients (9 males, 7 females) between 6 months and 19 years of age (mean \pm SD, 5.7 ± 6.5 years) undergoing allogeneic (15 patients) or autologous (one patient) bone marrow transplantation were enrolled in this study. Eight patients were affected by acute myelogenous leukemia, and two patients had chronic myelogenous leukemia. Five patients were affected by inborn errors of the immune system (three by familial hemophagocytic lymphohistiocytosis, one by Wiskott-Aldrich syndrome, and one by severe combined immunodeficiency) and one patient had thalassemia major. The age, sex, and weight of each recipient are reported in Table I, as well as details on donor compatibility, conditioning regimens, graft-versus-host disease, prophylaxis, transplant-related toxicity, and outcome. In all children, the conditioning regimen consisted of busulfan, given orally at a dose of 1 mg/kg every 6 hours for 16 doses (total dose, 16 mg/kg), associated with other drugs (Table I). The tablets were given by mouth with 50 ml water or by nasogastric tube. The moment of intake represented the zero point of the time axis. Anticonvulsant therapy (i.e., phenytoin) was used only in the 19-year-old male.

All patients were nursed in laminar air flow and received oral antibiotics, antibacterial skin care, and a low bacteria diet. Patients also received intravenous

commercial immunoglobulin preparations at dosages of 400 mg/kg every week starting two days before transplant and ending at day 70 after bone marrow transplantation. Empiric broad spectrum antibiotic therapy was started when children became febrile. Hematopoietic and lymphoid engraftment were documented by karyotype analysis on marrow cells and peripheral blood lymphocytes, red blood cell antigen phenotyping, and by HLA typing for patients with partially matched family donors.

Transplant-related toxicity was evaluated according to World Health Organization criteria.¹⁶ The renal and hepatic toxicity of busulfan was evaluated to compare pretransplantation and posttransplantation values of creatinine, BUN, total and direct bilirubin, AST, ALT, alkaline phosphatases, γ -glutamyltransferase, and cholinesterases. The difference between the two values (pretransplantation and posttransplantation) was statistically analyzed by the paired *t* test and by the Wilcoxon paired sample test.

Acute and chronic graft-versus-host diseases were classified according to previously described criteria.¹⁷⁻¹⁸ Hepatic veno-occlusive disease was diagnosed by use of previously described parameters.¹⁹ Interstitial pneumonia was diagnosed when bilateral interstitial alveolar infiltrates on chest x-ray film were associated with hypoxemia (PO_2 on room air ≤ 65 mm Hg).

Sample collection and drug analysis. Blood samples were collected in heparinized tubes immediately before and at $\frac{1}{2}$, 1, 2, 4, and 6 hours after the ninth dose of busulfan on the third day of therapy.

Samples were centrifuged and the plasma portion was separated and frozen at -20°C until the time of analysis. Busulfan plasma samples (300 μl) were assayed in duplicate by sensitive and specific high-performance liquid chromatographic (HPLC) technology described by Henner et al.²⁰ In brief, plasma busulfan was derivatized by sodium diethyldithiocarbamate to form 1,4-bis(diethyldithiocarbamoyl) butane, and the busulfan derivative was extracted into ethylacetate and dried in a Savant speed vacuum concentrator (Savant Instruments, Inc., Farmingdale, N.Y.). HPLC analysis was performed by use of a Supelcosil LC18 column, 5 μm , 25 cm \times 4.6 mm (Supelco, Inc., Bellefonte, Pa.). The mobile phase consisted of 83% methanol and 17% water, the flow rate was 1.3 ml/min, and the ultraviolet detector was at 251 nm.

The sensitivity limit of the assay was 50 ng/ml, and the intra-assay and interassay coefficients of variation were less than 8% over the entire range of the standard curve.

Table 1. Patient characteristics

Patient No.	Age (yr)	Sex	Weight (kg)	Disease*	Donor†	Conditioning regimen‡	GvHD prophylaxis§	Transplant-related toxicity¶	Outcome§
1	1.4	M	9	AML	Auto	BU, VP-16, L-PAM	—	m	Rel-Dead
2	14	F	38	AML	Sib	BU, CY-1, L-PAM	Cys	m	A&W
3	2.4	F	13	Thal	Sib	BU, CY-2	Cys + MTX	m	A&W
4	1.1	M	10	WAS	Mother (PMFD)	BU, ARA-C, CY-1	Cys	M-GvHD	Dead
5	3	F	12	FHL	MUD	BU, VP-16, ARA-C, CY-1	Cys + MTX	m	Reject-A&W
6	12.6	M	40	ALL	Mother (PMFD)	BU, CY-1, TAI, ATG	Cys	M-GvHD	Dead
7	10.2	F	36	AML	Sib	BU, CY-1, L-PAM	Cys	mV	A&W
8	0.5	M	5	AML	Father (PMFD)	BU, VP-16, L-PAM	Cys	m	Inf-Dead
9	1.2	M	9	FHL	Sib (PMFD)	BU, VP-16, TAI, CY-1	Cys	m	Inf-Dead
10	19.1	M	62	AML	Sib	BU, CY-1, L-PAM	Cys	M	A&W
11	0.5	F	5	FHL	Sib	BU, VP-16, TAI, CY-1	Cys	m	A&W
12	0.7	M	6	CML	Sib	BU, CY-1, L-PAM	Cys	mV	A&W
13	0.6	M	8	SCID	Father (PMFD)	BU, ARA-C, CY-1	TCD + Cys	m	Inf-Dead
14	16.2	M	28	AML	Sib	BU, CY-1, L-PAM	Cys	M	Rel-Dead
15	7.2	F	24	AML	Sib	BU, CY-1, L-PAM	Cys	m-IP	Rel-Dead
16	1.25	F	8	MCD	Sib	BU, CY-1, L-PAM	Cys	m	A&W

*AML, Acute myelogenous leukemia; Thal, thalassemia major; WAS, Wiskott-Aldrich syndrome; FHL, familial hemophagocytic lymphohistiocytosis; ALL, acute lymphoblastic leukemia; SCID, severe combined immunodeficiency; CML, chronic myelogenous leukemia; MCD, mast cell disease.

†Auto, Autologous bone marrow transplantation; sib, HLA-identical sibling; PMFD, partially matched family donor; MUD, matched unrelated donor.

‡BU, 4 mg/kg/day busulfan for 4 days; VP-16, 30 mg/kg etoposide; L-PAM, 140 mg/m² melphalan (single dose); CY-1, 60 mg/kg/day cyclophosphamide for 2 days; CY-2, 50 mg/kg/day cyclophosphamide for 3 days; ARA-C, 4 g/m²/day cytosine arabinoside for 2 days; ATG, TAI, thoracoabdominal irradiation 600 cGy single dose; 125 mg/4 kg antithymocyte globulin.

§Cys, Cyclosporine; MTX, methotrexate; TCD, in vitro T-cell depletion.

¶m, Mild mucositis; M-GvHD, moderate graft-versus-host disease; mV, mild veno-occlusive disease; M, moderate mucositis; m-IP, mild interstitial pneumonia.

§Rel, Relapse; A&W, alive and well; Reject, rejected; Inf, infection.

Pharmacokinetic analysis. Noncompartmental methods of pharmacokinetic analysis were used to determine the pharmacokinetic parameters for busulfan.²¹

The parameters considered were the peak concentration (C_{max}), that is, the highest observed concentration, and the time at which C_{max} occurred (t_{max}). Area under the plasma concentration-time curves (AUC) during the 6-hour dosing interval were calculated by the trapezoidal rule. Mean drug plasma levels over a dosing interval were calculated by dividing the AUC over the 6-hour dosing interval by 6 hours (C_{ss}). F is the fraction of the dose reaching the systemic circulation as unchanged drug after busulfan oral administration.

Total clearance after oral administration (CL/F) was determined by dividing the total administered dose (divided by body weight in kilograms) by the $AUC(0-6)$ over a single complete dosing interval. The terminal rate constant was obtained from the linear least-squares fit to the terminal log-linear portion of the plasma concentration data with the last three data points.

Simple linear regression analysis was performed by use of busulfan systemic exposure (AUC) and each of the pharmacodynamic response variables.

To assess whether patient characteristics determined variability in drug disposition or pharmacodynamic response, stepwise regression analyses were performed

Table II. Pharmacokinetic characteristics of busulfan after the ninth dose of 1 mg/kg ($n = 16$)

Patient No.	t_{max} (hr)	C_{max} (ng/ml)	C_{ss} (ng/ml)	AUC (ng · hr/ml)	CL/F (L/hr/kg)	$t_{1/2}$ (hr)
1	1	739.9	387.8	2327.1	-0.430	2.6
2	1	593.2	339.5	2037.1	0.491	2.8
3	0.5	649.4	348.6	2091.3	-0.478	1.9
4	2	499.9	264.2	1585.3	-0.631	1.4
5	2	268.8	150.4	902.6	-1.108	1.0
6	1	521.9	343.4	2060.6	0.485	2.7
7	1	824.9	367.5	2205.0	0.453	1.8
8	1	416.7	247.5	1485.2	-0.673	2.6
9	1	356.3	204.5	1226.9	-0.815	1.8
10	2	1157.2	689.1	4134.8	0.242	2.3
11	1	527.8	383.5	2301.1	-0.434	2.9
12	1	628.0	413.5	2480.7	-0.403	4.1
13	0.5	691.4	440.8	2644.9	-0.378	3.4
14	0.5	732.9	412.5	2475.2	0.404	3.2
15	1	824.5	551.7	3310.3	0.302	1.4
16	1	320.2	198.4	1190.5	-0.840	3.2
Mean \pm SD	4.1 ± 0.5	609.6 ± 225.3	358.9 ± 135.5	2153.6 ± 813.1	0.535 ± 0.226	2.4 ± 0.8

t_{max} , Time to reach maximum concentration; C_{max} , Maximum concentration; C_{ss} , steady-state concentration; AUC, area under the plasma concentration-time curve; CL/F, oral clearance; $t_{1/2}$, half-life.

in all patients with use of selected patient variables (age, sex, weight, body surface area, creatinine, BUN, total and direct bilirubin, AST, ALT, alkaline phosphatases, γ -glutamyltransferase, and cholinesterases).

Statistical analysis. Data are reported as the mean values \pm SD, unless otherwise noted. Data were analyzed by ANOVA with repeated measures, by paired t test, by the Wilcoxon paired sample test, or by the Pearson least-squares linear regression. A difference was considered statistically significant if the probability of erroneously reporting the null hypothesis of no difference was less than 5%.

Furthermore, regarding possible age-dependent disposition for busulfan, a local regression model with locally quadratic fitting was used when substantial curvature was present in the overall pattern of the data. In this case, graphic diagnostic checking on residuals and on the assumed (gaussian) error distribution were performed to accept or reject the model.²²⁻²³

RESULTS

The 16 pediatric patients studied had a mean weight of 19.6 ± 16.8 kg and a weight range from 5.0 to 62.0 kg. The mean age was 5.7 ± 6.5 years; the age range was from 6 months to 19.1 years. The mean body surface area was 0.69 ± 0.42 m², the body surface area range was from 0.25 to 1.30 m². Patient characteristics are listed in Table I.

Table II summarizes pharmacokinetic data of patients obtained on the third day of the preparative regimen (ninth dose of busulfan). The profile of mean plasma concentration-time curves after the ninth dose of busulfan are reported in Fig. 1. The t_{max} value was 1.1 ± 0.5 hour, C_{max} was 609.6 ± 225.3 ng/ml, AUC was 2153.6 ± 813.1 ng · hr/ml, C_{ss} was 358.9 ± 135.5 ng/ml, CL/F was 0.535 ± 0.226 L/hr/kg, and half-life ($t_{1/2}$) was 2.4 ± 0.8 hours.

Fig. 2 shows changes with age in busulfan CL/F, normalized for body weight.

We observed a statistically significant difference in the CL/F values between a group that included 10 patients with an age range from 6 months to 3 years and a group that included six patients with an age range from 7 to 19 years (0.619 ± 0.241 L/hr/kg and 0.396 ± 0.100 L/hr/kg, respectively; $p < 0.05$).

In the posttransplant period, total and direct bilirubin serum levels were significantly higher ($p < 0.05$) and cholinesterase levels were lower ($p < 0.001$) compared with pretransplant values.

We did not observe significant relationships between systemic exposure to busulfan (AUC) and renal or hepatic toxicity.

Of the 13 patients who received an allogeneic bone marrow transplant and survived more than 14 days after transplant, 12 (92.3%) achieved a complete engraftment. The patient who rejected the transplant (patient 5) was affected by familial hemophagocytic

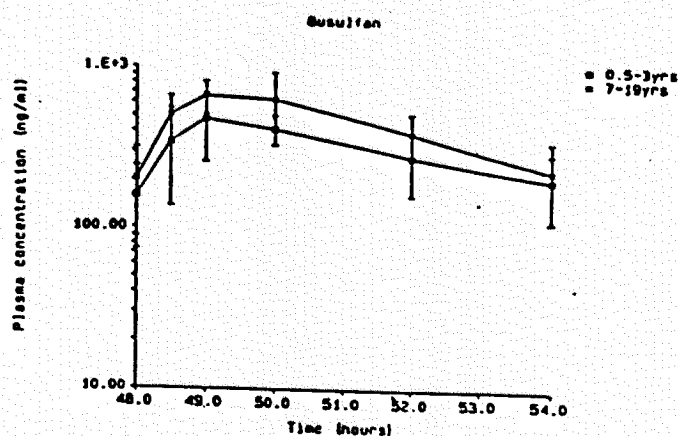


Fig. 1. Mean plasma concentration-time profiles of busulfan (1 mg/kg) during a dosing interval after the ninth dose in two groups of pediatric patients with different ages: 6 months to 3 years and 7 to 19 years.

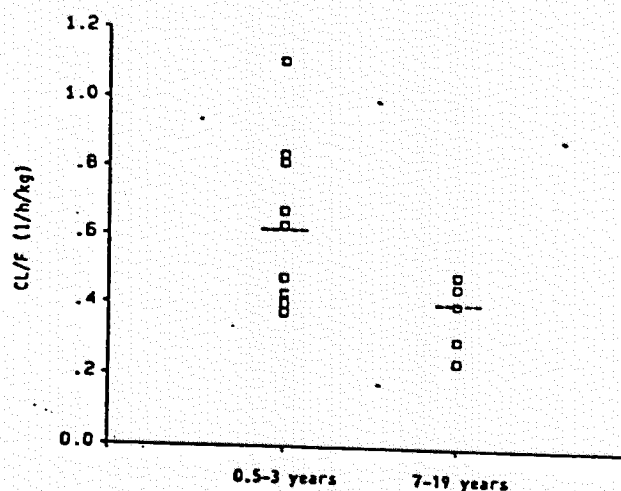


Fig. 2. Relationship between ages of patients and busulfan oral clearance (CL/F), normalized for body weight.

lymphohistiocytosis, a condition associated with a high incidence of rejection, and received a transplant from a matched unrelated donor. It should be emphasized that this patient had the lowest AUC and C_{max} values observed in our study.

Two patients (patients 8 and 9) died on days 6 and 9, respectively, without evidence of engraftment.

The median time to recovery granulocyte levels $>0.5 \times 10^9/L$ for 3 consecutive days was 23 days (range, 8 to 51 days) after transplantation, whereas platelets $>50,000 \times 10^9/L$ were reached after a median time of 45 days (range, 16 to 111 days) after bone marrow transplantation.

All patients had mild (75%) to moderate mucositis

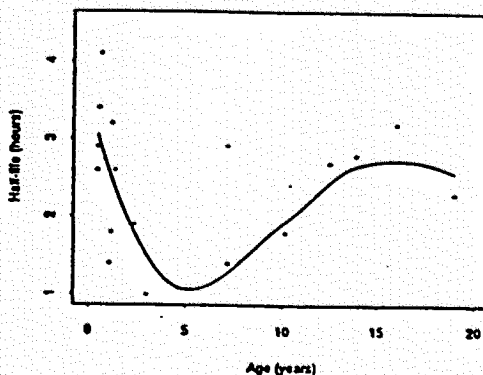


Fig. 3. Changes with age in the elimination half-life of busulfan: the curve was obtained with a local regression model by use of locally quadratic fitting.^{22,23}

(25%); severe mucositis, requiring preventive intubation, did not occur. Seizures and symptomatic hemorrhagic cystitis did not develop in any child. Hepatic veno-occlusive disease occurred in two (patients 7 and 12) of 16 patients (12.5%) and completely resolved with conventional treatment. Lethal interstitial pneumonia developed in one female patient (patient 15) about 1 year after transplant and 1 month after a marrow relapse. Incidences of acute and chronic graft-versus-host disease were 50% (6 of 12 evaluable patients) and 16.6% (2 of 12 evaluable patients), respectively. Two children had grade IV acute graft-versus-host disease. Three of nine patients affected by malignancies relapsed, all within 1 year after bone marrow transplantation.

As shown in Table I, eight patients have died. Three patients with acute myelogenous (two receiving an allogeneic bone marrow transplantation and one an autologous transplant) died of recurrent disease, associated with lethal interstitial pneumonia in one patient. Three patients died as a result of overwhelming infections and two died as a result of acute or chronic graft-versus-host disease (both receiving a partially matched, not T-cell depleted, transplant). Eight of 16 patients survived, and seven of those patients (two with nonmalignant and five with malignant disease) are free of their original disease, whereas the child who rejected the transplant is still alive in continuous complete hematologic remission.

DISCUSSION

Though based on a limited number of patients, our experience confirms that busulfan-containing condi-

tioning regimens seem to be sufficiently myeloablative and immunosuppressant to permit permanent engraftment (full donor chimerism detectable in 12 of 13 evaluable patients receiving an allogeneic bone marrow transplantation).

Notwithstanding higher bilirubin and lower cholinesterase serum levels in the posttransplant period, both transplant-related toxicity and mortality in the immediate posttransplant period were acceptable. A substantial advantage in the use of busulfan could be a shorter duration of neutropenia, which is related to a slower decrease in neutrophilic count after the conditioning regimen. Moreover, less severe mucositis might be related to busulfan-containing regimens compared with total body irradiation-containing regimens. Incidence of relapse (3 of 10 patients affected by malignancies) was also comparable to that observed after preparative regimens that included radiotherapy.

The physiologic processes that determine busulfan disposition undergo radical changes during biologic maturation. The maturation of an organism into an adult is successfully achieved only after completion of a series of intricate and interlocking events that proceed through a continuum.

Although most attention has been focused on newborns, age-dependent processes may also alter the efficacy of a drug in older infants and children.²⁴⁻²⁵

In general, there are changes in rate (usually slower) rather than in extent of absorption. We can therefore assume that the changes in oral clearance of busulfan reflect developmental changes in its metabolic rate.

The metabolic rate of hepatic-recovered busulfan-metabolizing enzyme systems is rapid in children beyond infancy, whereas in later childhood the rate of elimination decreases. Age-related differences in busulfan clearance were also observed when this parameter was normalized by both weight and body surface area.

Our findings on busulfan pharmacokinetics are also consistent with previously published pediatric studies. Grochow et al.²⁶ observed an oral clearance of 0.47 ± 0.20 L/hr/kg in children between 6 months and 3 years of age, which is significantly higher than values observed in adults receiving 1 mg/kg (0.15 ± 0.08 L/hr/kg). Moreover, an oral clearance significantly higher in young children compared with adults has been reported by Hassan et al.²⁷ and by Vassal et al.²⁸

It would appear from our data that starting from approximately 7 years of age busulfan clearance values begin to decrease and that older children have values approaching those observed in young adults.²⁶

As shown in Fig. 3, the $t_{1/2}$ values for busulfan during infancy decreased continuously until early childhood but were actually prolonged in older children. The local regression model of $t_{1/2}$ as a function of age shows a negative correlation for age < 5 years and a positive correlation for age > 5 years.

When we stratify the 10 patients up to 3 years of age into two groups, a lower, but not significantly different statistically, clearance value was calculated in infants from 6 months to 1 year of age versus 1- to 3-year-old children (0.47 ± 0.14 L/hr/kg versus 0.71 ± 0.25 L/hr/kg; $p > 0.05$). However, a significantly higher busulfan $t_{1/2}$ was observed in infants from 6 months to 1 year of age compared with the group of children from 1 to 3 years of age (3.2 ± 0.6 hours versus 2.0 ± 0.8 hours; $p < 0.05$), presumably reflecting differences in both hepatic-metabolizing capacity and distribution volume. Differences in busulfan distribution in these pediatric age groups could depend on the relative sizes of body water compartments, plasma protein binding capacity (about 55% in adults), and circulatory factors (blood flow to lipid-rich organs).

Cumulative frequency distribution for dose requirements among the two mean age groups, up to 3 years and 7 to 19 years, reveal at least a twofold change in dose requirement for each group, so that all individuals achieve therapeutic busulfan concentrations. Thus, theoretically, younger patients in late infancy and early childhood would be expected to require much higher doses of busulfan to obtain the same systemic exposure as adults.

Two recent studies by Vassal et al.²⁹ and by Yeager et al.³⁰ report that a higher dosage in young children is able to overcome the low level of systemic exposure attributable to age-dependent variation of busulfan pharmacokinetics, which confirms our observations.

The clinical consequence of the considerable inter-subject variability in the capacity to eliminate busulfan has not been clearly defined. Notwithstanding the limited number of cases included in this study, some observations can be drawn.

No significant relationship between systemic exposure to busulfan and drug effect were observed. However, increased drug metabolism could be partially responsible for the transplant rejection observed in a 3-year-old infant who had the lowest busulfan systemic exposure. Thus it is reasonable to hypothesize a relationship between the fastest clearance in this patient and the marrow rejection.

Given the progressive transformation into an adult pattern of drug disposition, closer monitoring is warranted during prepubertal and pubertal periods. This

may be especially important to avoid toxicity or inefficacy of busulfan. Prospective studies will be required to determine whether optimization of busulfan dosage on the individual pharmacokinetics of the drug will significantly improve response to therapy.

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associated toxicities may be multifactorial, the results of this study suggest that the decreased toxicity reported may be due to underdosing children based on busulfan regimens established in adults.

Several authors have expressed concern about engraftment failures in children who have received busulfan (8 to 16 mg/kg) and cytoxan as a preparative regimen.^{14,12,13} Hobbs et al¹³ reported that they changed their regimen to 80 mg/m²/d × 4, with a minimum dose of 16 mg/kg and a maximum dose of 20 mg/kg. Lucarelli et al¹² found that 5 of 24 children with β -thalassemia failed to engraft after treatment with 14 mg/kg, but only 1 of 16 treated at 16 mg/kg failed to engraft.

The results presented here suggest that achieving busulfan exposure in children equivalent to adults may require doses 50% to 100% greater on a weight basis. Providing pediatric doses on the basis of surface area^{20,22,23} will more closely

approximate adult exposures, but clearance rate normalized to body surface area in the children studied was still twice the clearance rate in adults. Since recurrent leukemia remains a significant problem for patients undergoing bone marrow transplantation,²⁴ achieving increased drug exposure may provide better antileukemic effect. In addition, higher doses may enhance the likelihood of donor engraftment. Since no pediatric phase I study has been done, we are performing a dose escalation study for busulfan in pediatric patients with pharmacokinetic monitoring. Additional information will be needed to provide dosing recommendations for older children and adolescents.

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The Impact of Obesity and Disease on Busulfan Oral Clearance in Adults¹

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³The abbreviations used were: BW, actual body weight; BSA, body surface area; IBW, ideal body weight; AIBW, adjusted ideal body weight; BMI, body mass index; CL/F, apparent oral clearance; AUC, area under the plasma concentration-time curve; C_{ss}, average steady-state concentration; GSH, glutathione; AML, acute myelogenous leukemia; MM, multiple myeloma; CML, chronic myelogenous leukemia; BrCa, breast cancer; RRT, regimen related toxicity;

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ABSTRACT

The apparent oral clearance (CL/F, mL/min) of busulfan was measured in 279 adolescent and adult patients. Significant ($p < 0.05$) determinants of CL/F by linear regression were: actual body weight (BW; $r^2 = 0.308$), body surface area (BSA; $r^2 = 0.286$), adjusted ideal body weight (AIBW; $r^2 = 0.285$), and ideal body weight (IBW; $r^2 = 0.196$); while body mass index (BMI), height, age, gender, and disease were less important predictors. CL/F (mL/min) for normal weight patients (BMI 18-27 kg/m²) was 16.2% lower ($p < 0.001$) than for obese patients (BMI 27-35 kg/m²). Expressing CL/F relative to BW or IBW did not eliminate statistically significant differences between normal and obese patients. However, busulfan CL/F expressed relative to BSA (110 ± 24 vs. 110 ± 24 mL/min/m², $p = 1.0$) or AIBW (3.04 ± 0.65 vs. 3.19 ± 0.67 mL/min/kg, $p = 0.597$) were similar in normal and obese patients. Breast cancer and multiple myeloma patients had approximately 13 and 17% lower mean busulfan CL/F expressed relative to either BW or BSA compared to patients with acute myelogenous leukemia. Routine dosing on the basis of BSA or AIBW in adults and adolescents does not require a specific accommodation for the obese. However, dosing based on BSA may be improved by considering CL/F differences in certain diseases. Adjusting dose for body size or disease does not diminish inter-patient variability sufficiently to obviate plasma level monitoring in many indications.

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